PC Code 057801

Data Evaluation Report on open literature: Pesticides and Birds– Mechanisms of Selective Toxicity
PMRA Submission Number: NA **EPA MRID Number**: 463643-15

Data Requirement:		
	PMRA DATA CODE	NA
	EPA DP Barcode	D311965
	OECD Data Point	NA
	EPA MRID	463643-15
	EPA Guideline	Nonguideline

Test material: Pirimiphos-methyl **Purity:** NA
Common name:

Primary Reviewer: Thomas M. Steeger, PhD, Senior Biologist **Date:** 12/28/2004
ERB IV, Environmental Fate and Effects Division, U. S. Environmental Protection Agency

Secondary Reviewer(s): Todd Phillips, PhD, Biologist **Date:** 1/12/2005
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CITATION: Brealey, C. J. C. H. Walker and B. C. Baldwin. 1980. A-esterase activities in relation to the differential toxicity of pirimiphos-methyl to birds and mammals. Pesticide Science 11: 546-554. Department of Physiology and Biochemistry, University of Reading, Whiteknights, Reading RG6 2AJ, and ICI Ltd. Plant Protection Division, Jealott's Hill Research Station, Bracknell, Berks, RG126EY, United Kingdom Submitted by Makhteshim Chemical Works, Ltd., 551 Fifth Ave., Suite 1100, New York, New York.

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EXECUTIVE SUMMARY:

Pirimiphos-methyloxon (2-diethylamino-6methylpryrimidine-4-yl dimethyl phosphate) the phosphate analog of pirimiphos-methyl, and paraoxon (diethyl 4-nitrophenyl phosphate) the phosphate analog of parathion were used as substrates to determine the esterase activity of plasma. Aryl groups released were measured by high-performance liquid chromatography or with a recording spectrophotometer. In a survey of 14 species of birds representing six different avian orders, the plasma esterase activity (expressed as nmol min-1 mL-1 of plasma) were always low, ranging from 0 - 71 for pirimiphos-methyloxon and from 0 - 0.63 for paraoxon. By contrast, mammalian activities were very much higher than these, and in no case was a sample of mammalian plasma less than 13 times more active than any sample of avian plasma using the same assay procedure. It is concluded that birds are deficient in A-esterase activity towards pirimiphos-methyloxon and paraoxon. The importance of this deficiency in determining the relatively high susceptibility of birds to these and other organophosphorous insecticides is discussed.

Reviewer's Comments:

Literature review shows that pyrimidine phosphorothionate insecticides (pirimiphos-methyl and diazinon) show at least a 10-fold higher acute oral toxicity in hens compared to rats and study sought to determine whether the differential toxicity is due to differences in detoxifying enzymes by comparing the hydrolytic activity in avian and mammalian plasma.

Small animals and birds were decapitation and blood was collected into heparinized tubes; large birds were bled from the wing vein or decapitated; jugular venous blood was collected from sheep and rabbits. Plasma stored at -10°C at which temperature esterase activity was believed to be stable for several months. Numbers, sex and weight (where reported) of animals used in study (Table 1) indicates that the number of animals was relatively low across species

Table 1. Avian and mammalian species, sex and body weight used in pirimiphos-methyloxon and paraoxon hydrolysis rate study.

Common Name	Scientific Name	Number, Sex[1], Weight (in kilograms)
Cormorant	*Phalacrocorax carbo*	3 M; 2.4 Kg
Shag	*Phalacrocorax aristotelis*	1 M. 1 F; 1.5 Kg
Canada Goose	*Branta canadensis*	4 F, 4 M
Japanese Quail	*Corturnix coturnix*	4 F, 4 M; 7 wks
Chicken	*Gallus gallus*	2 F; adults
Puffin	*Fratercula arctica*	2 F; 0.3 Kg
Razorbill	*Alca torda*	2 F; 0.34 Kg
Guillemot	*Uria aalge*	2F; 0.74 Kg
Black-headed Gull	*Larus ridibundus*	2 (sex uncertain)
Pigeon	*Columba livia*	3 (sex uncertain)
Blackbird	*Turdus merula*	2 M
Starling	*Sturnus vulgaris*	1 F, 1 M
Hedge sparrow	*Prunella modularis*	2 (sex uncertain)
Rook	*Corvus frugilesus*	2 F

Rat	Not reported	8M, 8 F; 0.25 Kg
Mouse	Not reported	3 F; 0.025 Kg
Sheep	Not reported	F (pool of 10)
Man	*Homo sapiens*	M (pool of 6)
Rabbit	Not reported	M (pool of 2)

[1] M=male; F=female

Pirimiphos-methyl and primiphos-ethyl were 100% pure and were obtained from ICI Chemical Company. Paraoxon was obtained from Koch Light while primiphos methyloxon was prepared by reaction of 2-diethylamino-6-methylpyrimidine-4-yl with dimethyl phosphorochloridate and anhydrous potassium carbonate. Paraoxon was unstable even when stored at -10°C.

Pirimiphosmethyloxon formation monitored using plasma samples (20 µL) incubated for either 1 or 4 minutes. Estimates of degradation of pirimiphosmethyloxon made by measuring the phosphate analog remaining in extracts of the incubation mixture. Paraoxonase measured by 4-nitrophenol release over a 5 to 10 minute period.

Plasma from both the rat and rabbit showed a time-dependent loss of p irimiphos methyloxon whereas plasma from Japanese quail and three passerine birds showed no measureable loss. The study asserts that the mammalian plasma contains an enzyme that destroys pirimiphos methyloxon which is not present in the quail and that the enzyme "appears to fit into the category of A-esterase with paraoxonase being one of the most studied of the A-esterases."

In a comparison of plasma A-esterase activities of 14 avian species towards pirimiphos methyloxon, and of nine species towards paraoxon and of five mammalian species towards both substrates, measurable activity for paraoxon was found only in one species of bird, *i.e.*, the Canada goose. Activity against pirimiphos methyloxon was detected in cormorants, shag, razorbill and guillemot at activities ranging from 2 to 71 nmoles min^{-1} mL^{-1} of plasma. However, in rats, mice, sheep and rabbits paraoxon ranged from 34 to 694 nmoles min^{-1} mL^{-1} plasma and activity toward pirimiphos methylparaoxon in rat, mice and sheep ranged from 920 to 2910 nmoles min^{-1} mL^{-1}.

The study concludes that 14 species of birds representing six different orders showed very much lower hydrolytic activity in vitro towards paraoxon and pirimimphos methyloxon than the five mammalian species investigated. They attributed this difference to the existence of much higher plasma A-esterase activity in the mammals than in birds. The authors went on to note that their results were consistent with other studies showing that "mammalian plasmas had high activity in the hydrolysis of diazinonoxon compared to very low or negligible rates for avian plasmas" and that the differential toxicity of organophosphates between mammals and birds was related to differences in A-esterase activity.